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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/726,211	10/04/96	TORMO M	UTXC:504

18N2/0708

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EXAMINER	
SCHWARTZMAN,R	
ART UNIT	**PAPER NUMBER**
1805	

DATE MAILED: 07/08/97

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/726,211	Applicant(s) Tormo et al.
	Examiner Robert Schwartzman	Group Art Unit 1805

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-20* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-20* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-20 are pending in this application.

Drawings

The drawings are considered to be informal because they fail to comply with 37 CFR 1.84(a)(1) which requires black and white drawings using India ink or its equivalent.

Photographs and color drawings are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) or (b)(1) is granted permitting their use as formal drawings. In the event applicant wishes to use the drawings currently on file as formal drawings, a petition must be filed for acceptance of the photographs or color drawings as formal drawings. Any such petition must be accompanied by the appropriate fee as set forth in 37 CFR 1.17(h), three sets of drawings or photographs, as appropriate, and, if filed under the provisions of 37 CFR 1.84(a)(2), an amendment to the first paragraph of the brief description of the drawings section of the specification which states:

> The file of this patent contains at least one drawing executed in color. Copies of this patent with color drawing(s) will be provided by the Patent and Trademark Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings have been satisfied.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 10-20 are drawn to a method of inhibiting a Bcl-2-associated disease, such as cancer or follicular lymphoma, by administering an antisense molecule targeted to Bcl-2 in association with a lipid. The claims are broadly drawn to the inhibition of any Bcl-2-associated disease or any Bcl-2-associated cancer. A search of the prior art indicates that method of treating a Bcl-2-associated disease has not been accomplished by targeting the expression of Bcl-2. Thus, the effectiveness of an antisense oligonucleotide targeted to Bcl-2 is unpredictable. This

unpredictability is amply demonstrated in the present specification, in which the antisense molecule decreased the viability of Johnson cells, which overexpress Bcl-2 due to a t(14;18) translocation but was ineffective in decreasing the viability of Raji or Jurkat cells, which also overexpress Bcl-2 but not because of a translocation. These three cell lines are derived from diseases (follicular lymphoma, Burkitt lymphoma and acute T cell leukemia, respectively) disclosed to be Bcl-2-associated and treatable by the claimed antisense oligonucleotide in the present specification (page 9, line 20-page 10, line 2). No guidance as to why certain Bcl-2-overexpressing cells are insensitive to Bcl-2 antisense treatment or how to predict which cells will be sensitive to antisense treatment is provided. The working examples disclosed in the specification involve the treatment of a follicular lymphoma cell line. No demonstration of the effectiveness of the claimed composition in a diseased cell *in vitro* or *in vivo* is disclosed. No disclosure of an art-recognized nexus between results obtained in Johnson cells and *in vivo* effectiveness is described. Prophetic examples for carrying out *in vivo* testing and treatment are disclosed but provide few details. The use of antisense oligonucleotides in disease therapy has yet to be demonstrated to be effective. Many oligonucleotides shown to be effective *in vitro* have been unsuccessful *in vivo*. Rojanasakul points out that the effective use of antisense oligonucleotides has been limited due to several problems associated with stability, cellular targeting, toxicity and affinity (pages 118-126). Based on the unpredictability in the area of the invention, the lack of working examples and guidance on in vivo effectiveness of the claimed composition in inhibiting a Bcl-2-associated disease, the broadness of the claims and the indication

in the prior art that antisense oligonucleotide therapy has yet to be successfully demonstrated, it would require undue experimentation by one of skill in the art to determine how to inhibit a Bcl-2-associated disease by administering an antisense polynucleotide targeted to Bcl-2.

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-20 are vague and indefinite as they are drawn to a polynucleotide that hybridizes to a Bcl-2-encoding polynucleotide but do not state any conditions under which hybridization takes place. Any two polynucleotides can hybridize under the appropriate stringency conditions. Therefore, the metes and bounds of the claims are not adequately defined. It is suggested that the claims be amended to be drawn to a polynucleotide complementary to a Bcl-2-encoding polynucleotide.

Claims 2-4 are vague and indefinite as they are dependent from claim 1 and refer to "said polynucleotide" or "the polynucleotide" but claim 1 is drawn to two different polynucleotides. It is unclear to which polynucleotide claims 2-4 are referring.

Claim 9 is vague and indefinite as it is drawn to a first polynucleotide but no second polynucleotide is mentioned. Furthermore, it is vague and indefinite as it is drawn to a composition but only discloses one product in the composition.

Claims 10-20 are vague and indefinite as it is not clear what is meant by inhibiting a disease (e.g., does it mean cure, slow down disease progression, decrease viability of diseased cells, etc.). Additionally, the claims are drawn to administering the polynucleotide/lipid association to a cell but provide no indication of what cell the association should be administered to. Furthermore, the method of claim 10 is incomplete as it is drawn to a method of inhibiting a Bcl-2-associated disease but the last step is administration of the association to a cell. Thus it does not appropriately refer back to the preamble.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Claims 1-6 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Evan.

Evan teaches the use of an antisense oligonucleotide targeted to Bcl-2 to prevent expression of the Bcl-2 protein (page 7, lines 10-29). The oligonucleotide is preferably targeted to the translation initiation site of Bcl-2 and preferably comprises the sequence of claimed SEQ ID NO: 1 (page 15, lines 16-23). The antisense oligonucleotide can be synthesized from an expression construct encoding the oligonucleotide (page 18, lines 26-30). The antisense oligonucleotide or expression construct is preferably delivered into cells as composition comprising a liposome (page 59, lines 6-7).

Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Reed.

Reed teaches the use of an antisense oligonucleotide targeted to Bcl-2 to prevent expression of the Bcl-2 protein (page 3, lines 2-22). The oligonucleotide is preferably targeted to the translation initiation site of Bcl-2 and preferably comprises the sequence of claimed SEQ ID NO: 1 (page 13, lines 2-5). The antisense oligonucleotide or expression construct is preferably delivered into cells as composition comprising a liposome or cationic lipids (page 14, lines 16-25).

Claims 1 and 2 are rejected under 35 U.S.C. 102(a) as being anticipated by Almazan et al.

Almazan et al. teaches an antisense polynucleotide targeted to Bcl-2. This polynucleotide was transfected into cells as a composition with cationic lipids.

Claims 1, 2, 5 and 6 are rejected under 35 U.S.C. 102(a) as being anticipated by Tormo et al.

Tormo et al. teaches an antisense polynucleotide targeted to Bcl-2. This polynucleotide was incorporated into liposomes.

Claims 1-6 and 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Green et al.

Green et al. teaches antisense oligonucleotides targeted to anti-apoptotic genes such as Bcl-2 (column 3, lines 51-67). The oligonucleotide is preferably targeted to a region including the translation start site of the anti-apoptotic gene (column 4, lines 46-51). The antisense oligonucleotide can be encapsulated into liposomes for administration (column 6, lines 60-63). Expression vectors that express the antisense oligonucleotide in a cell are disclosed (column 6, lines 8-10).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evan et al. or Reed et al. or Tormo et al. or Green et al. in view of Ledley.

Evan, Reed, Tormo et al. and Green et al. are applied as above. None of these references teach liposomes comprising phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine

or dioleolylphosphatidylcholine. Ledley et al. teaches (pages 628-630) lipid formulation for delivery of DNA. Ledley points out that formulations comprising neutral phospholipids such as dioleoylphosphatidylethanolamine facilitate highly efficient gene transfer. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use liposomes to transfer an antisense Bcl-2 polynucleotide into cells as taught by Evan or Reed or Tormo et al. or Green et al. having a formulation comprising the claimed phospholipids, motivated by the teaching of Ledley that such neutral phospholipids make highly efficient liposomes.

Conclusion

Claims 1-20 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Schwartzman whose telephone number is (703) 308-7307. The examiner can normally be reached on Monday through Friday from 7:00 AM to 4:00 PM.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703)-308-0196.

Papers relating to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-0294.

George C. Elliott

Robert A. Schwartzman, Ph.D.
July 7, 1997

GEORGE C. ELLIOTT
SUPERVISORY PATENT EXAMINER
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